Attorney Docket No. 1/844-3-C3

REMARKS

The present application is a Rule 60 continuation of prior application Serial No. 08/254,324 (hereinafter called the "parent").

An Office action was issued for the parent on 19 September 1995 (hereinafter called the "prior Office action"). As the prior Office action was made Final, the present continuation was filed, in lieu of filing a response. In order to advance prosecution, this communication will respond to the various issues presented in the prior Office Action.

In the parent, restriction had been required, under 35 USC 121, to one of the following four inventions:

I. Claims 1-9 and 11, drawn to compounds, compositions and method of use wherein m+n=2;

II. Claims 1-9, drawn to compounds, compositions and method of use wherein m+n=3;

III. Claims 1-9, drawn to compounds, compositions and method of use wherein m+n=4;

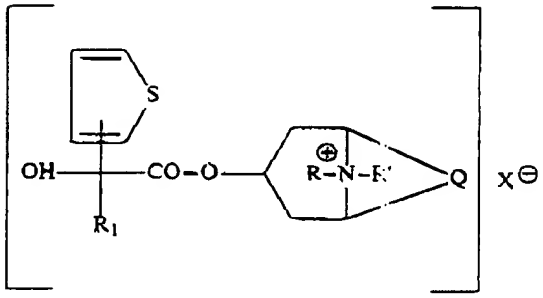
IV. Claims 10 and 12, drawn to processes for preparing compounds by transesterification.

This restriction requirement was made by telephone during a conversation, held on 2 November 1995, initiated by Examiner Datlow with the undersigned Attorney for Applicants. During that conversation the undersigned made a provisional election with traverse to prosecute claims directed to the invention of Group I.

In order to advance prosecution, Applicants will treat the present continuation as if the same restriction requirement had been made as in the parent. Accordingly, Applicants hereby once again elect to prosecute claims directed to the invention of Group I (compounds, compositions and method of use wherein m+n=2). This election is made without traverse. The claims have been amended to as to be restricted to subject matter within the scope of the election. Applicants reserve the right to file one or more divisional applications directed to non-elected subject matter.

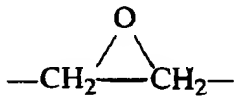
All of the claims pending in the parent (claims 1-12) have been canceled by amendment. New claims 13-28 have been added.

New claim 13 is directed to a genus of reduced scope, embracing compounds the formula



wherein

Q is a group of the formula $-CH_2-CH_2-$, -CH=CH- or



;

R and R' are each independently C_1-C_4-alkyl;

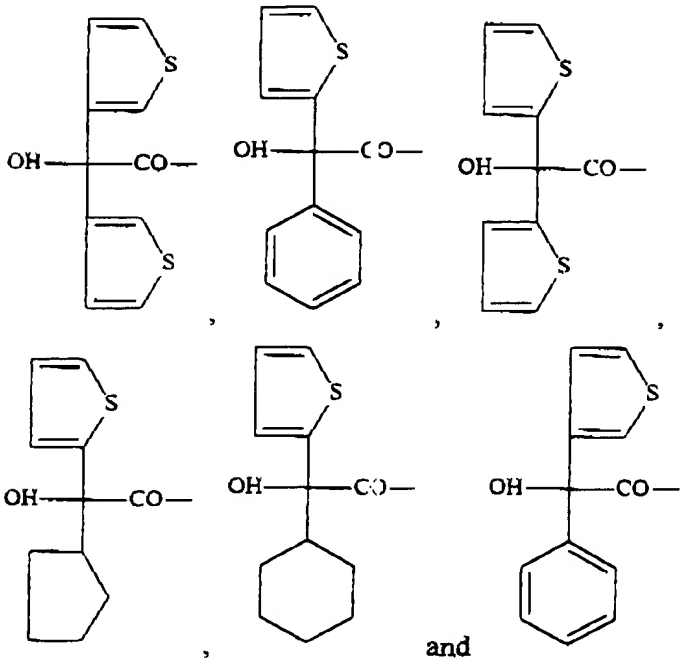
R_1 is thienyl, phenyl, cyclopentyl or cyclohexyl; and,

X^- is a physiologically acceptable anion.

This genus of claim 13 is concordant with the election. In the esters of claim 13, the alcoholic moiety is based upon tropan-3-ol, meaning that m+n=2.

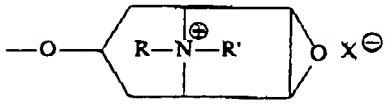
While the genus of claim 13 was not presented *per se* in the application as filed, the presentation of claim 13 does not introduce new matter. The specification can fairly be interpreted as describing the claimed genus. Thus, justification for claiming esters wherein the acid radical is as set forth in claim 13 is found at pages 3-4 of the specification, where it is stated that amongst the particularly suitable acid radicals are the groups of the formulae

Attorney Docket No. 1/844-3-C3

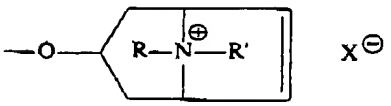


and

Justification for claiming esters wherein the alcohol radical is as set forth in claim 13 is found at page 5, lines 1-2 of the specification, where it is stated that the quaternary compounds are particularly suitable for therapeutic application, and at page 2, lines 18-23, where it is stated that the group -OA (the alcohol radical) preferably has the α-configuration and is derived from, inter alia, scopine, tropine or 6.7-dehydrotropine, or the β-configuration, as in pseudotropine and pseudoscopine, with the following being amongst the corresponding radicals which are specifically defined:

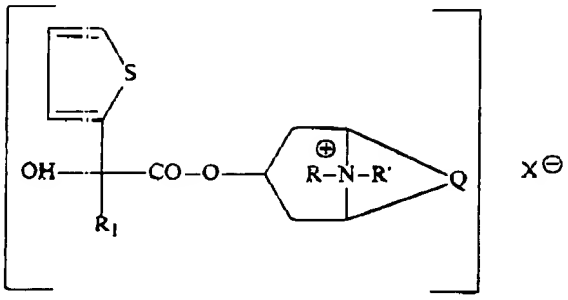


and



Finally, justification for limiting R and R' to C_1-C_4-alkyl is found at page 2, lines 1-4 of the specification.

New claim 14, which depends from claim 13, is directed to those compounds of the formula



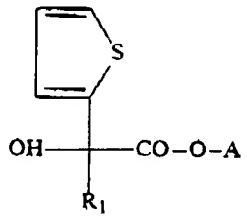
wherein
R is CH_3, CH_2H_5, n-C_3H_7, or i-C_3H_7;
R' is CH_3; and,
R_1, Q and X^- are as defined in claim 13.

The limitations regarding R and R' in claim 14 are based upon the preferences expressed in the specification at page 3, lines 4 and 5. The basis for limiting the thienyl group to attachment via the 2-position is that this group is so-attached in all of the quaternary compounds of the working examples. (See Table II, at pages 19-22 off the specification.)

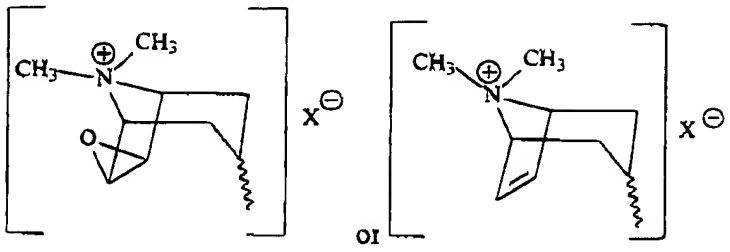
New claim 15, which depends from claim 14, is directed to those compounds wherein R_1 is thienyl. Justification for this limitation is found in the specification at page 2, lines 17-18, wherein in it is stated that preferred compounds are those wherein R_1 is thienyl.

New claim 16, which depends from claim 13, is directed to those compounds wherein X^- is limited to Br^- or CH_3SO_3. This is supported by the statement in the specification, at page 3, lines 17-18, that the anion is preferably Br^- or CH_3SO_3.

New claims 17 and 18 are directed to compounds of the formula

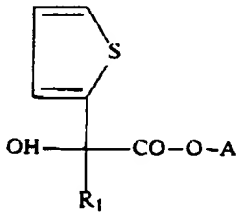


wherein R_1 is 2-thienyl and A is, respectively, a group of the formula



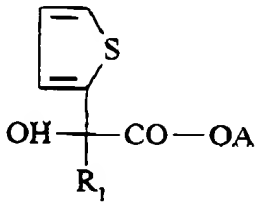
It should be noted that the conformation at the 3-position is not specified as being either α or β. Accordingly, claims 17 and 18 are intended to cover either isomer, or a mixture thereof. Both the α and β isomers are described in the specification. (See Compounds 1, 3, 35 and 37 in Table II on pages 19-21 of the specification.) The anion is left unspecified, in the manner supported by original claim 11.

New claims 19, 20 and 21 are directed to species of the formula



wherein R_1 is 2-thienyl and A is, respectively, 3α-(6β, 7β-epoxy)-tropanyl methobromide; 3α-(6β, 7β-dehydro)-tropanyl methobromide;and, 3β-tropanyl methobromide. These are Compounds 1, 3 and 36 of Table II, pages 19-21 of the specification.

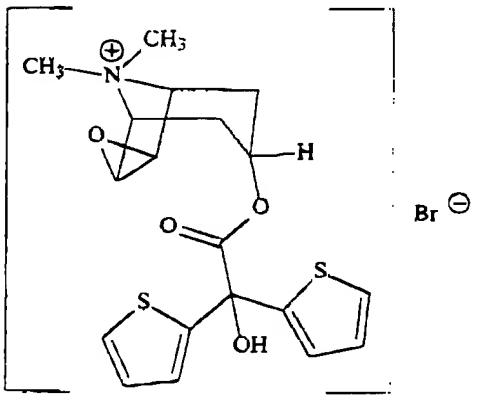
New claim 22 is directed to a compound of the formula



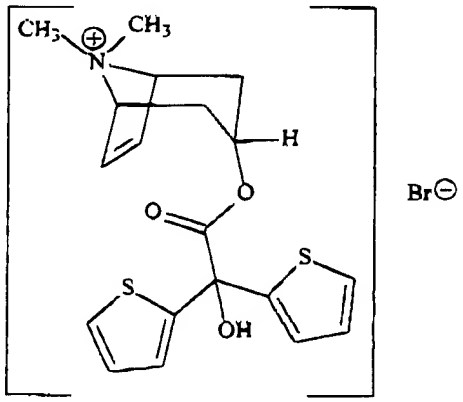
wherein R1 is cyclopentyl and A is 3α-(N-isopropyl)-nortropanyl methobromide and R_1 is cyclopropyl. This is Compound 31 of Table II, page 21 of the specification.

The species of claims 17-21 fall within the genus of claim 13, while the compound of claim 22 does not. The species of claims 17-22 all fall within the scope of the election.

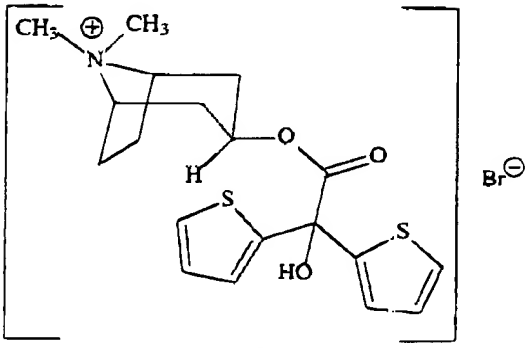
Because it may assist in comparing the new claims with the prior art, and in understanding the remarks which follow, the complete structural formulas for the four compounds of claims 19-22 are given below:



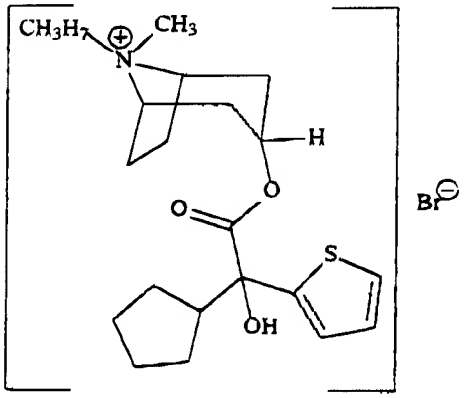
(claim 19)



(claim 20)



(claim 21)



(claim 22)

Claims 23, 24 and 25 are respectively directed to the treatment of chronic obstructive bronchitis, slight to moderately severe asthma and vagally induced sinus bradycardia through the administration of a compound in accordance with claims 13-22.

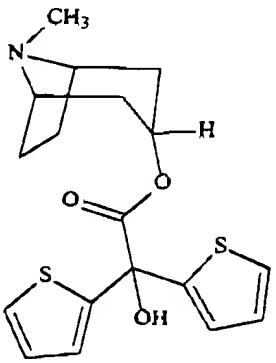
Claims 26, 27 and 28 are directed to pharmaceutical preparations, comprising compounds in accordance with claims 13-22, respectively suitable for (a) administration by inhalation, and the treatment of chronic obstructive bronchitis or slight to moderately severe asthma; (b) oral administration, and the treatment of vagally induced sinus bradycardia; and (c) intravenous administration, and the treatment of vagally induced sinus bradycardia.

The Abstract of the Disclosure had been objected to in the prior Office action, as lacking details about the major substituents and the utility. A revised abstract is presented by amendment herein. The revised abstract succinctly describes the subject matter of the new claims.

In the prior Office Action issued for the parent, claims 1-11 were rejected or objected to under 35 USC 112 or 35 USC 101, for a variety of reasons. These claims have been canceled and have been replaced by claims which are vastly different in nature. It is clear that these rejections and objections do not have any pertinence to the new claims.

In the parent, claims 1-3 were rejected under 35 USC 102(b) as being anticipated by Nyberg et al., "Investigations of Dithienylglycolic Esters", *Acta Chem. Scand.* **24** (1970) No. 5, 1590-1596.

Nyberg et al. disclose a compound of the following formula:



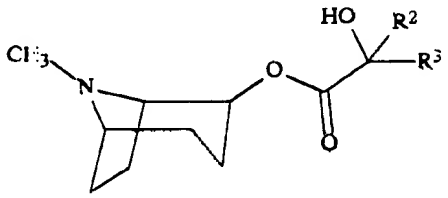
Due to the cancellation of claims 1, 2 and 3, this rejection is moot. Clearly, Nyberg et al. do not anticipate any of the new claims.

It should be noted, however, that the above-noted species of Nyberg et al. is structurally related to the compounds now being claimed. All of the compounds being claimed differ from the species of Nyberg et al. in that they are quaternary compounds, whereas that of Nyberg et al. is a tertiary amine. The species of claim 19 further differs from that of Nyberg in that the tropanyl ring has an epoxide bridge between positions 6 and 7, whereas that of Nyberg does not. The species of claim 20 further differs from that of Nyberg in that the tropanyl ring has a double bond between positions 6 and 7, whereas that of Nyberg does not. The species of claim 21 further differs from that of Nyberg in that the tropanyl ring is attached in the β orientation, whereas that of Nyberg is attached in the α orientation. The species of claim 22 further differs from that of Nyberg in that it contains one 2-thienyl moiety and one cyclopentyl moiety, whereas that of Nyberg has two 2-thienyl moieties.

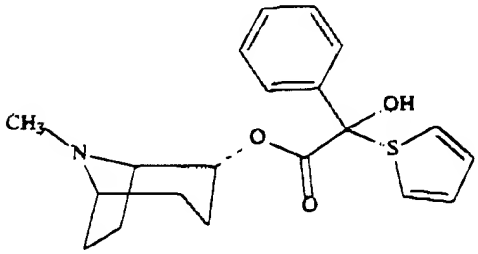
In the parent application, claims 1-4 and 6-9 were rejected under 35 USC 103 as being unpatentable over Atkinson et al. [*Journal of Medicinal Chemistry*, 1977, Vol 20, No. 12, 1612-1617] and Sterling Drug Inc. [Chemical Abstracts, Vol. 61, No. 1839f (1964)] in view of Grimminger et al. [U.S. Patent 4,855,422].

It is the earnest belief of the Applicants that the new claims are not rendered unpatentable by this same combination of references.

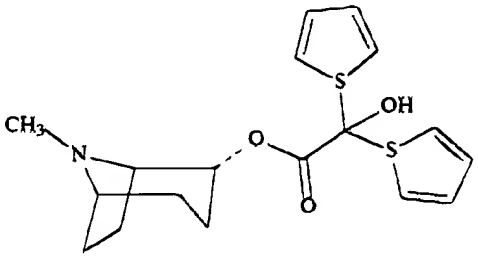
The prior Action states that the primary references of Atkinson et al. and Sterling Drug Inc. teach various esters of 2-tropanol as useful anticholinergic agents. The Action directs attention to compounds 5, 6, 18-22 and 31-32 of Table I of Atkinson et al., which are compounds of the formula



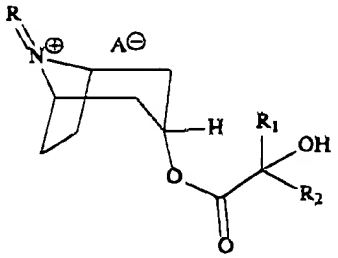
wherein R_2 is phenyl, cyclohexyl, or cyclopentyl, and R_3 is 2-thienyl. Attention is also directed to compounds disclosed by Sterling Drug having the formulas



and



The secondary reference, Grimminger et al., teaches 3-tropanol esters of the general formula



wherein, R is ,inter alia, C_3-C_9 alkylene, and R_1 and R2 are the same or different and are, inter alia, cyclohexyl, phenyl or thienyl. Specifically disclosed are compounds wherein R_1 and R_2 are both phenyl and R and the nitrogen atom to which it is attached, in a spiro system, together form, inter alia, pyrrolidin-1-yl (Example 1); pyrrolidin-3-yl (Example 2); isoindol-2-yl (Example 3); and, morphlin-4-yl (Example 4). These compounds are described as being anticholinergic spasmolytics, useful as broncholytics and in the treatment of asthmatic conditions. However, it should be noted that the Compounds of

Grimminger et al. are apparently not very potent broncholytics; In Example 8 it is noted that a dosage for a representative compound is 100 µg/inhalation.

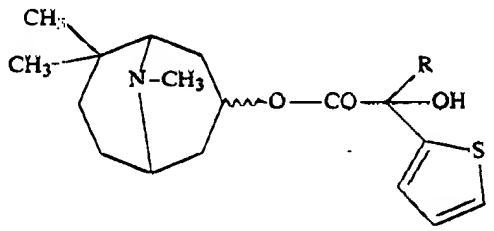
It is respectfully urged that one cannot properly combine the teachings of the primary and secondary references to obtain the compounds of the invention as presently claimed. All of the compounds embraced by the present claims have two distinguishing features: they are 3-tropanyl esters and they are N,N-di-lower alkyl quaternary amines. While combining the teachings of the primary and secondary references would arguably lead one skilled in the art to modify the compounds of the two primary references, to yield 3-tropanol esters, as the Examiner suggests, it would not lead one to make N,N-di-lower alkyl quaternary amines. The compounds of the primary references are tertiary amines and those of Grimminger et al. are spiro-type quaternary amines. None of the references teach N,N-di-lower alkyl quaternary amines.

Further, the compounds of claims 19 and 20 are also distinguished by the fact that their tropanyl rings respectively contain a 6β, 7β-epoxide bridge and 6β, 7β-unsaturation. These features are definitely not suggested by a combination of Atkinson et al., Sterling Drug Inc. and Grimminger et al. Accordingly, at the very least, claims 17 and 18 should be patentable over a combination of these references.

In the parent, claims 1-4 and 6-9 were additionally rejected under 35 USC 103 as being unpatentable over Yoneda et al. I and II. (U.S. Patents 3,673,195 and 3,808,263).

It is the earnest belief of the Applicants that the new claims are not rendered unpatentable by a combination of the two Yoneda et al. references.

Yoneda et al. I describes compounds of the formula

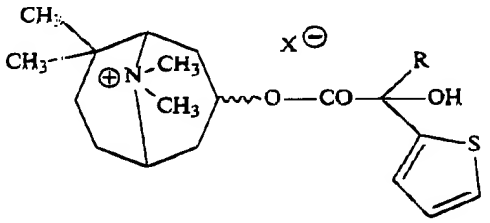


wherein R and the stereochemical conformation of the bicylco[3.3.1]nonan-3-ol moiety are as specified in the table below.

Example	R	Conformation
3	phenyl	α
4	phenyl	β
11	2-thienyl	α
12	2-thienyl	β
17	cyclohexyl	α
18	cyclohexyl	β

These compounds are described as being useful for the treatment of Parkinson's disease and as having anti-physostigmine and anti-tremorine activity, with a therapeutic activity comparable to that of atropine sulfate.

Yoneda et al. II describes compounds of the quaternary formula



wherein R and the conformation of the bicylco[3.3.1]nonan-3-ol moiety are the same as specified in Yoneda et al I. These compounds are described as possessing peripheral anticholinergic activity and being substantially free from central anticholinergic activity. More specifically, the compounds are described as having antispasmodic and anti-ulcer activity and as exhibiting anti-cholinergic activity about 22 times that of scopolamine butylbromide (Buscopan ®).

It is respectfully urged that the rejection based upon the two Yoneda et al. references, as explained in the prior action, does not apply to the new claims, as the new claims do not cover esters of 9-azabicyclo[3,3,1]non-3-ol. The new claims are limited to esters of 8-azabicyclo[3.2.1]octane. That is to say, the compounds of Yoneda are based upon the granatoline ring system whereas those of the invention, as now claimed, are based upon the tropine ring system. The compounds of both Yoneda et. al I and II are di-methyl substituted in the granatoline ring, whereas such substitution is not present in the tropine ring of the compounds of the invention. Moreover, based upon the comparison of the quaternary compounds of the Yoneda et al. II reference to scopolamine butylbromide (Buscopan®), which is not a bronchospasmolytic, it would appear that the compounds of Yoneda et al. II are not useful for the treatment of brochospasm, as are the compounds of the invention.

Attorney Docket No. 1/844-C3

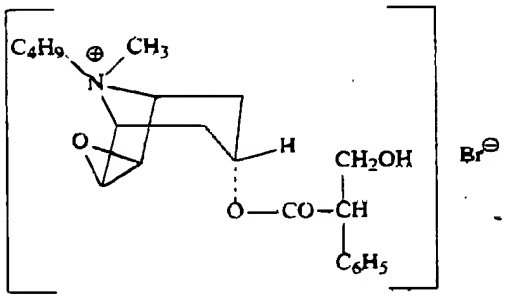
On the basis of the foregoing, it is respectfully urged that the new claims now pending (13-28) are supported by the disclosure and patentable over the art thus far made of record. Allowance of the claims and the application as a whole is respectfully requested.

#4

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR 1.56, Applicants wish to make the following information known to the Examiner. As this submission is being made by telecopier, copies of all references cited will be provided by mail, under separate cover, as will a Form PTO-1449 which lists these references.

1. The compound Buscopan® (N-butylscopolamine bromide), which has the following structural formula

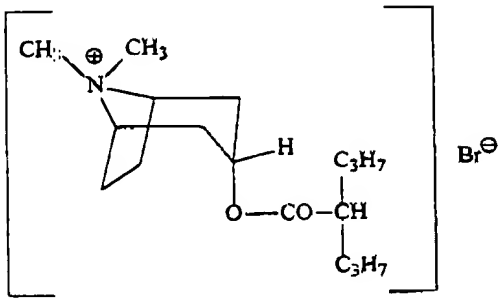


is mentioned in Yoneda et al. II (U.S. Patent 3,808,263, a reference made of record by the Examiner in the parent application.

Buscopan® (N-butylscopolamine bromide) is also described in the Merck Index, Tenth Edition, Merck & Co., Rahway, NJ (1983), p. 242.

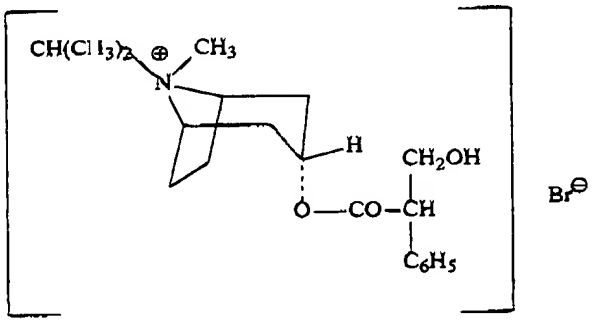
While structurally quite closely related to the compounds of the invention, especially the species of claim 19, Buscopan® (N-butylscopolamine bromide) and the compounds of the invention have very different pharmacological profiles. Scopolamine butylbromide (Buscopan®), is useful as an antispasmodic, but it is not a bronchospasmolytic. It is not useful for the treatment of bronchospasm, as are the compounds of the invention.

2. Valpin® (anisotropine methylbromide), which has the following structural formula,



is described in *The Pharmacological Basis of Therapeutics*, Sixth Edition, Goodman and Gilman, Editors, MacMillan Publishing Co., Inc., New York (1980), at page 130. While this compound is also structurally quite closely related to the compounds of the invention, especially the species of claims 21 and 22, Valpin® (anisotropine methylbromide) and the compounds of the invention have very different pharmacological profiles. Valpin® (anisotropine methylbromide), is useful for inhibiting gastric acid secretion and for reducing gastrointestinal motility, but it is not a bronchospasmolytic. It is not useful for the treatment of brochospasm, as are the compounds of the invention.

3. Atrovent® (ipratropium bromide), an anticholinergic bronchodilator, which has the following structural formula,



is mentioned at page 5, lines 9 and 10, of the specification and is described in the Merck Index, Tenth Edition, Merck & Co., Rahway, NJ (1983), p. 733. Concededly, this compound is structurally quite closely related to the compounds of the invention, especially the species of claims 21 and 22, and it possesses the same bronchospasmolytic activity as the compounds of the invention. Nevertheless, the Applicants are prepared to show by comparative test results that the compounds of the invention are, unexpectedly, longer lasting in their bronchospasmolytic effect than Atrovent® (ipratropium bromide).

Attorney Docket No. 1/844-3-C3

Respectfully submitted,

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August 14, 1995
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